REMARKS

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-3 and 21-25 as allegedly indefinite for referring to "MDA-9" rather than the sequence of the corresponding gene or protein. The Examiner stated that amending the claim to include a reference to a disclosed MDA-9 sequence would be sufficient to overcome this rejection.

Applicant has amended the claims to refer to the MDA-9 amino acid sequence disclosed in the application (SEQ ID NO:2) and respectfully requests that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected claims 1-3 and 21-25 as allegedly failing to meet the written description requirement. The Examiner based this rejection on the fact that the claims refer to "MDA-9" rather than the sequence of the corresponding gene or protein.

Applicant has amended the claims to refer to the MDA-9 amino acid sequence disclosed in the application (SEQ ID NO:2) and respectfully requests that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 1-3, 21 and 22 as allegedly obvious in view of Fisher (U.S. Patent 6,071,696) taken with Stromskaya et al. (Experimental and Toxologica Pathology 47:157, 1995) and Smith et al. (J. Biol. Chem. 270:28145, 1995). Applicant respectfully traverses this rejection.

In rejecting claims 1-3, 21 and 22 as obvious in view of Stromskaya et al., and Smith et al., the Examiner makes unwarranted assumptions and at least one factual error. Moreover, the Examiner's reasoning leads to conclusions that are at odds with the Applicant's experimental results.

This obviousness rejection is based on the Examiner's conclusion that, based on the teachings of the cited references, one of ordinary skill in art would have recognized that there is a correlation between MDA-9 expression and drug resistance. The Examiner's conclusion rests on four assertions: 1) Stromskaya et al. teaches that differentiation is correlated with drug resistance such that more differentiated cells are more drug resistant; 2) Fisher teaches that a combination of IFN-β and mezerin results in reduced MDA-9 expression, growth suppression and increased differentiation; 3) Fisher teaches that administration of IFN-β, IFN-α, or IFN-γ in the absence of mezerin results in upregulation of MDA-9 and growth suppression; and 4) Smith teaches that mezerin decreases drug resistance. From these assertions the Examiner argues that one of ordinary skill in the art would conclude that: (A) cells receiving IFN-β, IFN-α, or IFN-γ in the absence of mezerin (increased MDA-9 expression according to Fisher) would be more differentiated and more drug resistant; and (B) cells receiving IFN-β and mezerin (decreased MDA-9 expression according to Fisher) would be more differentiated and drug sensitive. According to the Examiner, because one of ordinary skill in the art would drawn these conclusions, one of ordinary skill in the art would find it obvious that MDA-9 expression is correlated with drug resistance.

The Examiner's conclusions are based on unwarranted assumptions and factual errors. For example, the Examiner assumes that the cells treated by Fisher with IFN-β are drug resistant. But Fisher does not measure or even mention the drug resistance of these cells. In addition, the Examiner assumes that the melanoma cells treated by Fisher with IFN-β and mezerin are drug sensitive, apparently because Smith et al. reports that mezerin can sensitize cells to vinblastine. But again Fisher does not measure the drug resistance of these cells. Moreover, the mezerin-treated cells studied by Smith et al. were not exposed to IFN-β and were breast cancer cells, not melamoma cells. The Examiner has not provided any rationale justifying the assumption that one could except the cells treated by Fisher to exhibit the same response to mezerin as the cells treated by Smith et al. despite the fact that the treatments differ and the cell types differ.

However, even if one were to agree with the Examiner's assumptions about the drug resistance of the cells treated by Fisher, the Examiner's conclusion is not warranted due to errors and inconsistencies in the Examiner's reasoning.

First, Fisher does not support the proposition that cells receiving IFN-β, IFN-α, or IFN-γ only (and no mezerin) are more differentiated. In fact, Fisher states precisely the opposite: "agents that suppress growth in H0-1 cells without inducing markers of differentiation, such as IFN-γ, elevate mda-9 expression" Fisher col. 16 at lines 25-27 (emphasis added). Referring to cells treated with only IFN-β or only mezerin, Fisher states that "cultures treated with a single agent are not terminally differentiated". Fisher col. 13, lines 57-58. Thus, nothing in Fisher suggests that IFN-β, IFN-α, or IFN-γ can induce differentiation. As outlined above, the Examiner's assumption that cells treated with IFN-β, IFN-α, or IFN-γ are drug resistant is unwarranted since the cited references provide no basis for making this assumption. Thus, the Examiner's assertion that cells treated by Fisher with IFN-β, IFN-α, or IFN-γ cells are both differentiated and drug resistant cannot be seen as reasonable to one of ordinary skill in the art.

Second, it is true that Fisher discloses that treatment with IFN-β and mezerin together induce differentiation and reduce MDA-9 expression. However, if one skilled in the art would conclude that increased differentiation correlates with increased drug resistance, as the Examiner asserts, then one skilled in the art would conclude that since reduced MDA-9 expression is associated with increased differentiation, then reduced MDA-9 expression is associated with drug resistance. Of course, this is exactly contrary to the results of the studies described in the current specification, where it was shown that MDA-9 expression is elevated in the a number of drug resistant cells lines. Thus, the Examiner's reasoning is not consistent with Applicants' experimental results

Third, if one were to follow the Examiner's reasoning that one skilled in the art would conclude from Fisher, Stromskaya et al. and Smith et al. that MDA-9 expression is correlated with drug resistance, one would conclude that cells treated with mezerin alone should have decreased MDA-9 expression because, according to the Examiner's reasoning, mezerin increases drug sensitivity. Yet, Fisher reports that "mda-9 expression is unaffected in H0-1 cells grown for

4 days in 10 ng/ml of MEZ, even though growth is reduced by ~74%" Fisher at col. 15, lines 3-5. Thus, the Examiner's reasoning is not consistent with Fisher's experimental results.

In view of the forgoing, Applicant respectfully requests that the rejection of claim 1-3, 21 and 22 as obvious in view of Fisher, Stromskaya et al. and Smith et al. be withdrawn.

The Examiner rejected claim 1-3 and 21-25 as allegedly obvious in view of Fisher, Stromskaya et al. and Smith et al. taken with Zamboni et al. (Clin. Cancer Res. 4:743, 1998) and Zhou et al. (Drugs 44 (Suppl. 4):1, 1992).

According to the Examiner, Fisher, Stromskaya et al. and Smith et al. render obvious the in vitro screening of compounds to identify potential modulators of drug resistance based on MDA-9 expression and Zamboni et al. and Zhou et al. teach that it is important to confirm in vitro results in animals.

As discussed above, Fisher, Stromskaya et al. and Smith et al. do not render obvious the *in vitro* screening of compounds to identify potential modulators of drug resistance based on MDA-9 expression. Neither Zamboni et al. nor Zhou et al. provide what the combination Fisher, Stromskaya et al. and Smith et al. lacks, i.e., a teaching or suggestion that MDA-9 expression is correlated with drug resistance. Instead, Zamboni et al. and Zhou et al. simply describe the results of various in vivo studies on certain chemotherapeutic agents. Thus, Fisher, Stromskaya et al., Smith et al., Zamboni et al. and Zhou et al., no matter how combined, cannot render claims 1-3 and 21-25 obvious.

Contrary to the Examiner's assertion the no combination of the cited references teaches or suggests a method for identifying candidate modulators of drug resistance by determining the effect of a test compound on MDA-9 expression.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be withdrawn.

Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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